REMARKS/ARGUMENTS

Claims 31, 33, 35-40, and 42-57 are pending in the application. Independent claims 31 and 42 are amended hereby. Support for the amendment to claim 31 can be found in the specification at, *e.g.*, paragraphs 0259, 0288 and 0292 of the published application (US 2004/0062712). Support for the amendment to claim 42 can be found in the specification at, *e.g.*, paragraphs 0081 and 0252 of the published application.

Applicants address each of the Examiner's rejections below in the order presented in the Office Action (OA).

Priority

The Examiner has maintained a denial of Applicants' priority claim, as set forth in the Office Action of August 3, 2006. *See* p. 2 of the OA. Applicants reiterate that the issue of priority does not currently appear to be material to the grounds of rejection raised by the Examiner, but reserve the right to address the issue if it becomes relevant in future proceedings.

Claim Rejections - 35 U.S.C. §112, 1st Paragraph

Claims 31, 33, 35-38, 54, and 56 are rejected under 35 U.S.C. 112, 1st paragraph because the specification allegedly does not provide enablement for screening an agent for a therapeutic activity. *See* paragraph bridging pp. 2-3 of the OA. The Examiner states that because the claims fail to specify any pathology for the teleost used to screen for the therapeutic activity, the activity identified by this component of the claimed screening method is only *potentially* therapeutic, and the actual ability of the agent to diminish or eliminate pathological signs or symptoms when administered to a subject exhibiting the pathology can not be determined. *See* p. 3, penultimate paragraph, and paragraph bridging pp. 3-4 of the OA.

Without agreeing with the Examiner's position, Applicants have amended independent claim 31 to replace "therapeutic activity" with "pharmacological activity." Pharmacological activity is defined in the specification as "a property of an agent that indicates that the agent is, or may be, useful for treatment and/or prevention of a disease." *See* paragraph 0292 of the specification.

Applicants submit that the recitation of "pharmacological activity" addresses the Examiner's concern regarding whether the activity identified for the agent by the latter component of the claimed screening method is *actually* therapeutic, and consequently removes any need to perform the assay on a teleost having a particular pathology. Because pharmacological activity is, *or may be*, useful for treating or preventing a disease, it is not necessary that the teleost used in this component of the claimed screening method have any particular phenotype in order to assess the pharmacological activity of the agent. Rather, the skilled artisan can select a particular property (*e.g.*, modulation of a specific cellular pathway) that he or she believes is indicative of an activity that is, or may be, useful to treat or prevent disease, and then use the claimed method to screen an agent for the activity. The response that is indicative of a pharmacologial activity can be defined by controls selected by an investigator with regard to the desired pharmacological activity of interest. Thus, the skilled artisan will be able to use the claimed method as a generally applicable screening assay for evaluating an agent for both a toxic activity and a pharmacological activity.

As noted in response to the Office Action of February 8, 2008, the specification includes a general description of what a response "indicative of pharmacological activity" can include. *See* paragraph 0292 of the specification. For example, responses indicative of a pharmacological activity can include increases or decreases in the number of cells or the concentration of a cellular marker, such as an enzyme or a secondary metabolite. Such responses can also include modulation of a cellular pathway, or the promotion or inhibition of a physiological event such as cell growth or differentiation. *Id.* As discussed above, a response indicative of a pharmacological activity indicates to the investigator that the agent is, or may be, useful for treating or preventing a disease. The skilled investigator can readily determine the appropriate response indicative of a desired pharmacological activity to suit his or her needs and thus adapt the screening assay to his or her purposes without undue experimentation. Thus, the specification provides sufficient guidance to enable one of skill in the art to perform the claimed screening method to assess an agent's toxicity and pharmacological activity.

As requested by the Examiner in the first paragraph of page 5 of the Office Action, Applicants note that combined screening of pharmacological and toxic activity is

discussed in the application at, for example, paragraphs 0259 and 0288. Paragraph 0259 states that "[t]he methods for screening agents for toxic activity described herein can be combined with other methods of the present invention...." Although this paragraph indicates that the other methods *include* screening for angiogenesis or cell death activity, the term "including" is not limiting, and screening for pharmacological activity is another method of the present invention. *See*, for example, paragraph 0015, which states that "[t]he invention further provides methods of screening an agent for a pharmacological activity." Moreover, paragraph 0288 states that "[a]gents showing good [pharmacological] activity are also tested for toxicity and lethality." These passages provide descriptive support for the claimed combination assay to screen an agent for both toxicity and a pharmacological activity, and would have enabled the skilled artisan to perform the claimed method without undue experimentation.

Based on the foregoing, Applicants submit that the claimed invention is enabled by the specification. There being no art rejections regarding claims 31, 33, 35-40, 54 and 56, Applicants respectfully submit that the present amendment places these claims in condition for allowance. Thus, Applicants respectfully request entry of this amendment.

Claim Rejections - 35 U.S.C. §112, 2nd Paragraph

The claim rejections under 35 U.S.C. §112, 2nd paragraph appear to have been withdrawn. *See* p. 5, last paragraph of the 112-2nd paragraph rejection. However, the Examiner also states that "[t]he following new rejection is necessitated by amendment," but does not set forth any additional information identifying the rejection. *See* p. 5, 2nd paragraph of the 112-2nd paragraph rejection. In light of the foregoing, Applicants respectfully request that the Examiner clearly withdraw this ground of rejection, or set forth any alleged deficiency with particularity.

Claim Rejections - 35 U.S.C. §102(b)

Claims 42-46, 53, and 57 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Mizell *et al.*, *Int. J. Dev. Biol.*, 41:411-423 (1997). The Examiner states that Applicants previous arguments were not persuasive because Mizell discusses administration of the agent through culture media. *See* p. 6, last paragraph of the OA.

Applicants respectfully submit that the Examiner may have misunderstood the prior amendment to claim 42, and have therefore further amended claim 42 to make it explicitly clear that the agent is added to culture media *already* containing the teleost. As acknowledged by the Examiner, Mizell reports placing an embryo into a drop containing the agent. *See* p. 6, last paragraph of the OA. Thus, Mizell does not teach adding the test agent to culture media already containing the teleost, as claimed. It is well established that for a prior art reference to anticipate a claimed invention, the prior art reference must teach each and every element of the claimed invention. *See* MPEP §2131. Applicants submit that Mizell does not teach each and every element of the claimed invention. In particular, Mizell does not teach addition of the test agent to culture media already containing the teleost, as claimed. Thus, Mizell does not anticipate the claimed invention. Because each of the other claims identified by the Examiner depends directly or indirectly from independent claim 42, each of the dependent claims is patentable over Mizell for at least the same reason discussed above.

Based on the foregoing, Applicants respectfully request entry of the present amendment and withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C. §103(a)

Claims 47, 48, and 50-52 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Mizell, *supra*, in view of Terse *et al.*, *Toxicon*, 31:913-919 (1993), and claim 55 is rejected as allegedly being unpatentable over Mizell in view of Maccubbin *et al*, *Aquatic Toxicology* **9**:277-286 (1986), or Black, *Aquatic Toxicology* **11**:129-142 (1988), or Marty *et al.*, *Aquatic Toxicology* **17**:45-62 (1990). The Examiner dismissed Applicants' arguments, presented in the Amendment of February 8, 2008, as irrelevant (*see* p. 7, 4th paragraph of the OA), stating that Mizell teaches addition of the agent to culture media (*see* p. 8, 1st paragraph of the OA).

As discussed above, the Examiner appears to have misunderstood the amendment to claim 42 that was set forth in the response of February 8, 2008, and which Applicants have further clarified in the present amendment; namely, that the test agent is added to culture media *already* containing the teleost.

Mizell does not teach addition of the test agent to culture media already containing the teleost, as claimed. Rather, Mizell reports microinjection of both zebrafish and medaka, as well as contacting dechorionated zebrafish with a droplet of "various chemical pollutants" in a 10 cm Petri dish. In the latter method, a 250 µl droplet of a solution comprising one or a combination of test agents is placed in a Petri dish and a single embryo is placed in the droplet. After a 30 minute period of exposure, the embryo is removed from the droplet, rinsed three times in embryo rearing solution (ERS), and transferred to a Petri dish half-filled with ERS. *See* p. 421 of Mizell. There is no discussion that indicates that the test agents are added to the culture medium already containing the teleost, as claimed. Rather, the embryo is placed into the droplet comprising the test agent and thereafter washed and placed in culture media.

Terse reports *in vitro* assays of murine and bovine cell cultures in multi-well plates and does not discuss *in vivo* screening methods in any capacity, let alone addition of a test agent to culture media containing a teleost. Moreover, Terse teaches away from the presently claimed method, indicating that "[t]here is a need to develop and validate *in vitro* assays for toxicity in order to *reduce the use of laboratory animals*." *See* p. 913, 1st paragraph (emphasis added). One of skill in the art seeking to modify an *in vivo* screening assay, as claimed by Applicants, would not have looked to Terse to do so in light of the authors' stated objective of reducing the use of laboratory animals.

Maccubbin reports placing a 1 µl droplet of DMSO/agent solution directly on the surface of a teleost egg. *See* p. 279 of Maccubbin. In the Maccubbin method, the eggs are contacted with the DMSO droplet while lying on a gauze pad in a Petri dish, and then, following an exposure period to ensure absorption of the solution, removed and placed in aerated spring water. *See* p. 280 of Maccubbin. Maccubbin does not discuss addition of a test agent to culture media already containing a teleost, as claimed.

Black discusses the method of Maccubbin as useful for overcoming difficulties in achieving adequate exposure to chemicals via a noninvasive technique. *See* p. 137-138 of Black. Black also reports that sensitivity of trout embryos to chemical carcinogens was originally demonstrated by immersing eyed-stage ova in an aqueous solution of aflatoxin B_1. *See* p. 130 of

Black, first full paragraph. Black does not discuss addition of a test agent to culture media already containing a teleost, as claimed.

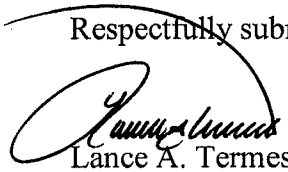
Marty reports exposure of Medaka eggs to various chemical solutions by randomly distributing the eggs into solutions comprising the agents, followed by repeated rinsing of the eggs in embryo rearing medium (ERM) and placement in ERM. *See* p. 47 of Marty. Marty does not discuss addition of a test agent to culture media already containing a teleost, as claimed.

Clearly, none of the references cited by the Examiner discusses a method in which the test agent is added to culture media already containing a teleost, as claimed by Applicants. Rather, in each case, the reference discusses a method in which the teleost is immersed in a solution of the agent or contacted by applying a drop of the solution to its surface. Thus, no reference of record teaches this element of the claimed invention, and no rationale is provided by the Examiner to support a *prima facie* case of obviousness in the absence of this element within the cited references. Notably, independent claim 42 has not been rejected as unpatentable under 35 U.S.C. 103(a) over any combination of the foregoing references. Because each of the rejected claims depend directly or indirectly from claim 42, each is patentable over the references of record for at least the reasons discussed above.

Based on the foregoing, applicants respectfully request withdrawal of this ground of rejection.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Lance A. Termes
Reg. No. 43,184

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
LAT:ylm
61860389 v1